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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,974	02/21/2002	Joseph Rubinfeld	12636-263	2253

21971 7590 06/29/2004

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EXAMINER	
MCINTOSH III, TRAVISS C	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 06/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,974	RUBINFELD ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-21,23 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-21,23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed April 19, 2004 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claim 1 has been amended.

Claims 17, 22, 24, and 26-53 have been canceled.

Remarks drawn to rejections of Office Action mailed January 23, 2004 include:

112 2nd paragraph rejections: which have been overcome by applicant's amendments and have been withdrawn.

103(a) rejection which has been maintained for reasons of record.

An action on the merits of claims 1-16, 18-21, 23, and 25 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 19, 2004 has been entered.

Claim Rejections - 35 USC § 103

The rejection of claims 1-16, 18-21, 23, and 25 under 35 U.S.C. 103(a) as being unpatentable over Rubinfeld (US Patent 6,191,119) in view of Achterrath (US Patent 6,403,569), is maintained for reasons of record.

Claim 1 is drawn to a method of treating cancer in a patient comprising administering either 9-nitro-20(S)-camptothecin or 9-amino-20(S)-camptothecin for a period of time during which 5-fluorouracil is not being administered nor is present in the patient, then administering 5-fluorouracil (5-FU) to the patient, wherein the period of time in which the 5-FU is not being administered is at least 1 day. Claims 2-6 provide that the 20(S)-camptothecin is administered at least 1-5 days before the 5-FU, respectively. Claims 7-11 provide that the 20(S)-camptothecin is administered at least 1, 2, 3, 4, or 5 to 90 days before the 5-FU. Claims 12-16 provide that the 20(S)-camptothecin is administered at least 1, 2, 3, 4, or 5 days after the 5-FU. Claims 18-20 provide that the 20(S)-camptothecin is administered between 2, 3, or 4 to 90 days before or after the 5-FU is administered, and wherein the 20(S) camptothecin is administered within 2, 3, or 4 days of when the 5-FU is administered. Claims 21 and 25 provide various cancers which the patients have, and claim 23 limits the camptothecin to 9-nitro-20(S)-camptothecin.

Rubinfeld teaches of methods for treating cancer comprising the use of combination therapy by coadministering to the patient a 20(S)-camptothecin (including 9-

nitro-20(S)-camptothecin) in combination with for example, a synergistic antimetabolite, such as 5-fluorouracil (column 2, lines 37-67). It is noted that Rubinfeld defines coadministration to mean the administration of more than one therapeutic in the course of coordinated treatment to achieve clinical outcome, such coadministration may also be coextensive, that is, occurring during overlapping periods of time (column 5, lines 54-62).

What is not taught by Rubinfeld is to specifically use 5-fluorouracil, nor to allow for at least 1 day between the administration of the 5-fluorouracil and the 20(S)-camptothecin. Moreover, it is noted that while Rubinfeld does not specifically acknowledge the 1 day between the administration of the active agents, they do indeed recognize the alternative as an option, wherein they state that "such coadministration *may also be*, that is, occurring during overlapping periods of time". This clearly sets forth that the coadministration may occur during overlapping periods of time, as well as during non-overlapping periods of time.

Achterrath teaches a method of treating cancer comprising administering at least one camptothecin derivative in combination with 5-fluorouracil (column 1, lines 8-15).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the methods of the prior art and obtain the methods as claimed in the instant application with the references before them. The prior art teaches the use of 20(S)-camptothecins in combination therapy with 5-fluorouracil in treating cancers. Moreover, the prior art teaches of the synergistic effects of the combination therapy (see '119, column 4, lines 64-68) and that the active agents may be administered in delayed release forms which may delay their release from about 1 hour to about 6 months (see '119,

column 7, lines 36-39). Modifying the prior art methods and optimizing the time frames required between the active agents administration is seen to require nothing more than routine skill in the art, and one of ordinary skill in the art would be appraised of methods of determining the optimum time frames for that art recognized active agents to be administered.

Applicant's arguments filed April 19, 2004 have been fully considered but they are not persuasive. Applicants argue that nowhere in the references is there a teaching or suggestion to administer the water insoluble 9-nitro-, or 9-amino-20(S)-camptothecin and 5-fluorouracil sequentially by following the regimen of claim 1. Applicants additionally argue that Achterrath teaches a camptothecin, 5-FU, and folinic acid in combination for treating cancer, and not the specific sequential treatment regimen as set forth in claim 1. However, the examiner notes that Achterrath is cited to show that camptothecin derivatives are know to be effective when used in combination with 5-FU. Rubinfeld teaches that 9-amino-20(S)-camptothecin and 9-nitrocamptothecin were found to have high activity against various cancer models (column 2, lines 1-16). Moreover, Rubinfeld teaches to administer the camptothecin derivatives in combination with a multitude of compounds, including 5-FU (column 2, lines 52-55) which afford synergistic effects to the treatment, thus bridging the nexus and making obvious the combination of 5-FU and the 9-amino- and 9-nitro-camptothecin derivatives. Moreover, Rubinfeld teaches that the combinations of therapeutics may be administered by a variety of routes, and may be *administered or coadministered* in any conventional dosage form. Moreover, Rubinfeld teaches that coadministration is defined to mean the administration of more than one therapeutic in the course of a coordinated treatment to achieve a clinical outcome,

wherein such coadministration *may also be coextensive*, that is, occurring during overlapping periods of time (see column 5, lines 54-62). Thus, the fact that coadministration is set forth by the phrase "may also be coextensive" indicates that in addition to administration being coextensive, it is also contemplated as being non-coextensive, or occurring during non-overlapping periods of time. The use of the claimed active agents in combination are known in the art to provide synergistic effects in cancer therapy and non-coextensive therapy is contemplated. One of ordinary skill in the art would be appraised of methods of determining the optimum time frame for administering the art recognized active agents to a patient for cancer therapy. Absent of a side by side comparison of the prior art methods and the methods as instantly claimed, as in the form of a 132 declaration, showing the effectiveness of the instantly claimed method and the prior art methods, applicant's arguments are not persuasive.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Traviss C. McIntosh III
June 24, 2004

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623